Thalamic mechanisms underlying alpha-delta sleep with implications for fibromyalgia

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1Department of Mathematics and Statistics, Boston University, Boston, Massachusetts; 2Harvard Medical School, Boston, Massachusetts; 3Division of Sleep and Circadian Disorders, Brigham and Women’s Hospital, Boston, Massachusetts; and 4Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women’s Hospital, Boston, Massachusetts

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Vijayan S, Klerman EB, Adler GK, Kopell NJ. Thalamic mechanisms underlying alpha-delta sleep with implications for fibromyalgia. J Neurophysiol 114: 1923–1930, 2015. First published August 5, 2015; doi:10.1152/jn.00280.2015.—Alpha-delta sleep is the abnormal intrusion of alpha activity (8- to 13-Hz oscillations) into the delta activity (1- to 4-Hz oscillations) that defines slow-wave sleep. Alpha-delta sleep is especially prevalent in fibromyalgia patients, and there is evidence suggesting that the irregularities in the sleep of these patients may cause the muscle and tissue pain that characterizes the disorder. We constructed a biophysically realistic mathematical model of alpha-delta sleep. Imaging studies in fibromyalgia patients suggesting altered levels of activity in the thalamus motivated a thalamic model as the source of alpha activity. Since sodium oxybate helps to alleviate the symptoms of fibromyalgia and reduces the amount of alpha-delta sleep in fibromyalgia patients, we examined how changes in the molecular targets of sodium oxybate affected alpha-delta activity in our circuit. Our model shows how alterations in GABA<sub>B</sub> currents and two thalamic currents, I<sub>k</sub> (a hyperpolarization-activated current) and a potassium leak current, transform a circuit that normally produces delta oscillations into one that produces alpha-delta activity. Our findings suggest that drugs that reduce I<sub>k</sub> conductances and/or increase potassium conductances, without necessarily increasing GABA<sub>B</sub> conductances, might be sufficient to restore delta sleep. Furthermore, they suggest that delta sleep might be restored by drugs that preferentially target these conductances in the thalamus; such drugs might have fewer side effects than drugs that act systemically.

Fibromyalgia is a syndrome marked by chronic diffuse pain, fatigue, and sleep disturbances. Individuals with fibromyalgia have a higher incidence of alpha-delta sleep (Moldofsky et al. 1975; Roizenblatt et al. 2001), the abnormal co-occurrence of alpha activity (8- to 13-Hz oscillations) and delta activity (1- to 4-Hz oscillations) resulting from the intrusion of alpha activity into the delta activity that occurs during slow-wave sleep. There is evidence that alpha-delta sleep may exacerbate the pain of fibromyalgia patients (Roizenblatt et al. 2001), and it may even be the source of their pain, since artificially inducing alpha activity during slow-wave sleep produces fibromyalgia-like symptoms in healthy individuals (Moldofsky et al. 1975). Thus knowing how alpha-delta sleep arises may be a key step in understanding the pathophysiology of fibromyalgia and in developing treatments for the condition. Currently the neural mechanisms that give rise to alpha-delta sleep are poorly understood.

Here we present the first biophysically based mathematical model for the occurrence of alpha-delta sleep. We used the neural abnormalities observed in fibromyalgia and the molecular targets of drugs used in its treatment in the development of our model. Manifestations of fibromyalgia at the neural level include abnormal thalamic activity (Kwiatek et al. 2000; Mountz et al. 1995) and a lower stimulus threshold for the activation of the pain pathway (Cook et al. 2004; Gracely et al. 2002), so we started with a somatosensory thalamic model. Sodium oxybate, whose molecular targets are GABA<sub>B</sub>, potassium channels, and a nonspecific cation current (Madden and Johnson 1998; Schweitzer 2004), has been shown to reduce the incidence of alpha-delta sleep in fibromyalgia patients (Moldofsky et al. 2010; Scharf et al. 2003). We found that, by altering the conductances of the molecular targets of sodium oxybate, our model can be switched from production of normal delta sleep to production of alpha-delta sleep.

GABA<sub>B</sub> currents are thought to be important in the induction of normal delta sleep (Destexhe et al. 1996; Terman et al. 1996). However, our model suggests that the actions of sodium oxybate on potassium leak channels and hyperpolarization-activated current (I<sub>k</sub>) may be more important than its actions on GABA<sub>B</sub> and may even be sufficient to restore normal delta sleep. Our model also suggests that drugs that specifically target the somatosensory thalamus may be effective in treating fibromyalgia. Since no animal models of fibromyalgia exist, our model provides a much-needed tool for understanding what makes current fibromyalgia drugs efficacious and thus for potentially finding more effective drugs.

Materials and Methods

Model motivation. Our aim was to develop a biophysically realistic neural network that could account for the dynamics of alpha-delta sleep. We started with a thalamic model for awake alpha oscillations (Vijayan and Kopell 2012) because imaging studies suggest that thalamic activity is abnormal in fibromyalgia patients (Kwiatek et al. 2000; Mountz et al. 1995) and because the alpha activity seen during alpha-delta sleep is more like awake alpha than sleep spindles (11–16 Hz); the alpha activity seen during alpha-delta sleep has a longer duration than spindles and does not wax and wane as spindles do (Roizenblatt et al. 2001). Our starting model, based on a model by Destexhe et al. (1996), could also generate delta oscillations. Since fibromyalgia patients suffer from somatic pain (Clauw 2014), our model of alpha-delta sleep incorporated the cellular properties of thalamic somatosensory nuclei (Lörincz et al. 2008).

Details of model. Our model consists of single-compartment Hodgkin-Huxley neurons that are governed by the equation...
where $C_M$ is the membrane capacitance, $I_M$ the membrane currents, and $I_{syn}$ the synaptic currents. The model consists of reticular nucleus (RE) cells and thalamocortical (TC) cells (Fig. 1A). RE cells provide inhibition to TC cells via $\text{GABA}_{\alpha}$ and $\text{GABA}_{\beta}$ connections and to themselves via $\text{GABA}_{\alpha}$. TC cells in turn excite RE cells via $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) connections. All cells in the network contain standard potassium, sodium, and leak currents. All cell types also contain T-type calcium channels, and TC cells possess $I_h$ channels (see Vijayan and Kopell 2012 for additional details). Incorporated into the model is a specialized subset of TC cells, called high-threshold thalamocortical (HTC) cells, which have been reported to comprise $\sim 15–25\%$ of TC cells in thalamic somatosensory nuclei and which experimental studies suggest burst at the alpha frequency at relatively depolarized membrane potentials (greater than $-60$ mV) (Hughes et al. 2004; Lőrincz et al. 2008, 2009); they are the putative generators of thalamic alpha. The bursts are thought to be mediated by a variant $I_T$ channel that bursts at relatively depolarized membrane potentials; we call these channels $I_{THT}$ (Hughes et al. 2004; Lőrincz et al. 2008, 2009). HTC cells are also weakly coupled via gap junctions. For further model details see Vijayan and Kopell (2012) and Vijayan et al. (2013).
Our model does not include a cortical component. The incorporation of such a component would require additional experimental studies illuminating the mechanisms underlying cortical delta and alpha oscillations. We reason that a thalamic model suffices since JExperimental work suggests that alpha oscillations manifest at the thalamic level (Hughes et al. 2004; Lörincz et al. 2008, 2009), 2) pharmacological prevention of HTC cell bursting at the alpha frequency disrupts cortical alpha (Lörincz et al. 2009), and 3) delta oscillations can be generated at the level of the thalamus (Dossi et al. 1992; McCormick and Pape 1990; Steriade et al. 1993) and have been reported in the thalamus during non-rapid eye movement (NREM) sleep (McCarley et al. 1983; Steriade et al. 1971, 1996; Tsoukatos et al. 1997; Weyand et al. 2001). All neurons received Gaussian noise to ensure model robustness. That is, each neuron received a random amount of current (normally distributed) at each time point, so that the sum of the currents for a given neuron was not simply a function of the parameter values chosen and the state of the neuron but had a component that fluctuated randomly. This ensured that the qualitative behavior of our network is not sensitive to the precise values taken on by the currents under a particular set of parameter values.

We simulated EEG using the activity of TC and HTC cells, the two cell populations in our circuit that project to the cortex. TC and HTC cells drove a representative downstream pyramidal cell via AMPA connections, and the membrane potential of this pyramidal cell was used to calculate the EEG (see McCarthy et al. 2008 for additional details).

Alpha-delta simulation. Oscillatory activity at the delta frequency was achieved by setting parameter values similar to those used by Destexhe et al. (1996). The critical manipulation, as in Destexhe et al. (1996), was setting GABA_A conductances to zero so that GABA_A timescales dominated (Destexhe et al. 1996; Terman et al. 1996; Vijayan and Kopell 2012). The Destexhe et al. (1996) model does not include HTC cells since it predates their discovery. Although HTC cells are a subset of TC cells, HTC cells differ in the conductance values of some of the currents they have in common. In particular, since HTC cells contain additional currents and are gap junction connected we used different potassium and leak currents in HTC cells, and since HTC cells are more weakly coupled to RE cells than TC cells are (Lörincz et al. 2009) we used smaller GABA conductances in RE-HTC cell connections than in RE-TC cell connections (Vijayan and Kopell 2012 for additional details).

Sodium oxybate, which reduces alpha-delta sleep in fibromyalgia patients (Moldofsky et al. 2010; Scharf et al. 2003), potentiates GABA_A conductances, reduces Ih conductances, and increases potassium conductances (Madden and Johnson 1998; Schweitzer 2004). To determine the parameter values that produce alpha-delta activity, we started with delta oscillation conditions and altered these three conductances in the direction opposite to that effected by sodium oxybate: We reduced the GABA_A conductances of the entire network by 50%, increased Ih, and reduced potassium leak current (Ileak). All these changes act to depolarize neurons in our network. When depolarized, HTC cells produce awake alpha oscillations (Lörincz et al. 2008), and so our model uses HTC cells to produce alpha activity. However, depolarization of RE and TC cells causes these cells to stop bursting at the delta frequency, so such depolarization would result in the disappearance of delta activity in our model. Thus in our alpha-delta model we selectively depolarized HTC cells by restricting the changes in Ih and Ileak to HTC cells. We also consider the alternative case in which the entire somatosensory thalamus is depolarized.

We conjecture that selective depolarization of HTC cells may in fact occur in fibromyalgia patients. Our reasoning is as follows: The pain pathway in fibromyalgia patients appears to be overactive, since stimuli that are not considered painful by healthy individuals are perceived as painful by fibromyalgia patients. Since pain afferents project to the somatosensory thalamus and thalamic activity is thought to be abnormal in fibromyalgia patients, we reasoned that somatosensory thalamic activity may be altered in fibromyalgia patients. In particular, we reasoned that the increased drive in the pain pathway may lead to increased depolarization of neurons in the somatosensory thalamus. Since HTC cells, at depolarized membrane potentials, are thought to be the generators of thalamic awake alpha, and since fibromyalgia patients experience the intrusion of alpha activity in their delta sleep, we conjectured that in fibromyalgia patients HTC cells may be depolarized. Selective depolarization of HTC cells could occur if the anatomical inputs to HTC cells differ from those to TC cells; however, at present the projections of the pain pathway to HTC cells are unknown and require investigation.

**RESULTS**

**Phenomenology.** Slow-wave sleep (stage 3 NREM sleep) consists of prominent delta oscillations (Fig. 1C, gray trace, data from subject 12). However, in patients with fibromyalgia, alpha oscillations can intrude into slow-wave sleep (Fig. 1, B and C, black trace, data from subject 3; Moldofsky et al. 1975; Roizenblatt et al. 2001). Note that these oscillations are relatively continuous (Fig. 1, B and D) and do not show the waxing and waning characteristic of sleep spindles (Fig. 1E).

**Baseline delta oscillations.** We first tested that our computational model could generate the activity pattern seen during normal slow-wave sleep: delta activity without prominent alpha oscillations. Indeed, when the model parameters are set to values similar to those used by Destexhe et al. (1996), all cell populations in our network (RE, TC, and HTC) burst at the delta frequency (Fig. 2, A and B). The TC and HTC cells, the two cell populations that project to the cortex, both burst at ~2.62 Hz (Fig. 2C), and the simulated EEG shows prominent delta oscillations (Fig. 2D). The delta timescales are imposed on the TC and HTC cells via inhibitory GABA_A connections from the RE cells. The TC cells rebound spike, causing the RE cells to spike via excitatory AMPA connections, and the cycle begins anew.

The delta oscillatory regime in our model is robust but can be broken if either TC or HTC cells initiate bursts significantly more quickly than the other. Such differences in initiation times can occur, for example, if either population has a significantly stronger Ih conductance, since Ih helps in initiating bursts. In this case the cell type that initiates bursts faster acts via RE cells to suppress the other cell type, preventing its firing.

**Simulated alpha-delta sleep.** As described in MATERIALS AND METHODS, we adjusted the parameters of our network in a direction opposite to that effected by sodium oxybate. After these adjustments, HTC cells burst at the alpha frequency (10.76 Hz; Fig. 2, E–G) and TC cells burst at the delta frequency (3.67 Hz; Fig. 2, E–G). The simulated EEG (Fig. 2H) shows alpha activity riding on top of delta activity as is seen in the human data (Fig. 1D). HTC cells burst at the alpha frequency because they become relatively depolarized (greater than ~60 mV) and because they have a variant I_Ih channel, which we call I_IhTHT, that mediates the alpha frequency bursts.
and is active at relatively depolarized membrane potentials (Vijayan and Kopell 2012). The relative level of depolarization of the HTC cells determines their bursting frequency (Fig. 2). We then explored whether one of the molecular targets of sodium oxybate might be more critical than the others to the restoration of delta sleep. Starting with our model of alpha-delta sleep, we adjusted the conductance of each of the targets of sodium oxybate independently. In all of the stated manipulations (e.g., change in \( I_h \), \( I_{KL} \), or \( GABA_B \) conductances), we considered the action of sodium oxybate on the entire network.

**Restoring GABA\(_B\).** When we restore only \( GABA_B \) levels to those at which the entire network oscillates at the delta frequency, the HTC cells alternate between periods of silence and periods of bursting at the alpha frequency (Fig. 3, A and B). The relatively long periods of silence occur after the RE cells fire (Fig. 3, A and B) since, because of the increase in \( GABA_B \) conductance, RE cells exert more inhibition on HTC cells. The TC cells continue to burst at the delta frequency, but at a slightly lower frequency because of the increased inhibition via \( GABA_B \). The simulated EEG in this case consists of delta activity with a higher-frequency activity (12.21 Hz) riding on top of it (Fig. 3C).

**Restoring \( I_h \).** We then reduced only \( I_h \) values to the levels used during delta oscillations. At these values HTC cells become silent (Fig. 3, E and F). This is in part because \( I_{HTT} \) channels, which help to mediate the high-threshold bursts in HTC cells, are moved out of their operating range because of the hyperpolarizing effect of the reduction in \( I_h \). In addition, the reduction in \( I_h \) impairs the ability of HTC cells to initiate high-threshold bursts. The simulated EEG in this instance shows prominent delta oscillations (Fig. 3G); that is, the decrease in \( I_h \) conductance restores slow-wave activity.

**Restoring \( I_{KL} \).** When we restore only \( I_{KL} \) conductance values to those used during delta oscillations, RE and TC cells still fire at the delta frequency. However, HTC cells are silenced because the increased potassium conductance pulls HTC cells toward the potassium reversal potential, preventing them from initiating bursts (Fig. 3, I and J). As in the case of \( I_h \) reduction, the simulated EEG in this case shows prominent delta oscillations (Fig. 3K).

If we reduce only \( I_h \) to 5%, 10%, 20%, or 50% below the levels used in our delta conditions or increase only \( I_{KL} \) or only \( GABA_B \) to 5%, 10%, 20%, or 50% above the levels used in our delta conditions our results remain qualitatively the same (Fig. 3, D, H, and L).

**Restoring \( GABA_B \), \( I_h \), and \( I_{KL} \).** Of course, if we simultaneously change the \( GABA_B \), \( I_h \), and \( I_{KL} \) conductance values to those used during delta conditions, all cell types oscillate at the delta frequency and the activity resembles that in Fig. 2, A–D. If we reduce \( I_h \) to 5% below the levels used during delta conditions and increase both \( I_{KL} \) and \( GABA_B \) to 5% above the levels during delta conditions, TC cells oscillate at the delta frequency (Fig. 4, A and B) but HTC cells are silent (Fig. 4, A and B), so the entire network, except for HTC cells, oscillates at the delta frequency and the simulated EEG consists of delta oscillations (Fig. 4C). Our results remain qualitatively the same if we simultaneously change all three currents by 10%, 20%, or 50% in the appropriate direction beyond the levels used in our delta conditions (Fig. 4D). Thus, in our model, sodium oxybate brings either the entire network or all but HTC cells back to the condition.
The alpha-delta conditions are for TC/H6126 mus, rather than just the subset of HTC cells, is at a relatively slow-wave sleep. It is not essential that the thalamus be the generator of delta activity; what is critical is that in the thalamus may be just as effective in treating fibromyalgia as drugs that target only HTC cells to the levels used during delta activity. Thus drugs that target only \( I_h \) or only \( I_{KL} \) in HTC cells, which can restore delta sleep from alpha-delta sleep. In addition, in our model, alpha-delta sleep is abolished when only \( I_h \) conductances are reduced or only \( I_{KL} \) conductances are increased during alpha-delta conditions. We move each conductance in turn to delta conditions and further in the direction that reduces the membrane potential (for \( I_h \) this means reducing the conductance, and for \( I_{KL} \) and GABA\(_B\) it means increasing the conductance). −20 on the \( x \)-axis means a 20% change in conductances in the hyperpolarizing direction relative to delta values. A–C: same as Fig. 2, A, B, and D, when only GABA\(_B\) is increased from alpha-delta conditions to delta conditions. The parameter values changed from alpha-delta conditions are for TC \( g_{GABA_B} = 0.4145 \) mS/cm\(^2\) and for HTC \( g_{GABA_B} = 0.0138 \) mS/cm\(^2\). D: TC (black dots) and HTC (gray symbols) firing frequencies when network activity is moved from alpha-delta conditions by increasing only GABA\(_B\) to delta conditions and beyond. Note that HTC cells fire in a nested fashion; we plot both the slower modulating frequency (gray dots) and the frequency of the faster nested oscillation (gray triangles). E–H: same as A–D when only \( I_h \) is decreased from alpha-delta conditions. The parameter value changed from alpha-delta conditions is for HTC \( g_{KL} = 0.009 \) mS/cm\(^2\). I–L: same as A–D when only \( I_{KL} \) is increased from alpha-delta conditions. The parameter value changed from alpha-delta conditions is for HTC \( g_{KL} = 0.0225 \) mS/cm\(^2\).

### Discussion

**Model implications for fibromyalgia treatment.** Our results suggest that alpha-delta sleep may arise via the selective depolarization of HTC cells (via alterations in \( I_h \) and \( I_{KL} \) conductances) or by the depolarization of the entire somatosensory thalamus; in the latter case delta activity arises from the cortex. Simultaneously increasing GABA\(_B\) conductances, decreasing \( I_h \) conductances, and increasing \( I_{KL} \) conductances can restore delta sleep from alpha-delta sleep. In addition, in our model, alpha-delta sleep is abolished when only \( I_h \) conductances are reduced or only \( I_{KL} \) conductances are increased in HTC cells to the levels used during delta activity. Thus drugs that target only \( I_h \) or only \( I_{KL} \) in HTC cells, which generate the alpha activity in all our model alpha-delta conditions, might be sufficient to prevent alpha-delta sleep and its deleterious effects, providing relief to fibromyalgia patients. More broadly, our model suggests that drugs that act locally in the thalamus may be just as effective in treating fibromyalgia as drugs that act systemically. Such drugs would likely be preferable since they may have fewer side effects. One approach in the development of drugs for fibromyalgia would be to use an animal model to look for drugs that preferentially alter the conductances of HTC cells. Such a drug might work...
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by optimally altering the conductances of the potassium leak or $I_h$ channel subtypes found on HTC cells versus other cell types.

We note that in the simulations where only $I_h$ or only $I_{KL}$ is manipulated, HTC cells stop producing alpha activity by being silenced and do not produce delta activity. It is possible that in order to experience the full beneficial effects of delta sleep, the entire thalamic network, including HTC cells, must burst at the delta frequency, as it does in our delta model. Although in vitro studies suggest that, like standard TC cells, HTC cells are capable of bursting at delta at relatively hyperpolarized membrane potentials, whether they do so during normal slow-wave sleep is not known (Hughes et al. 2004). Since fibromyalgia is a multifaceted disorder and likely has effects on multiple brain circuits, it is possible that not all drugs provide their therapeutic effects via the circuit and mechanisms that we model here.

In all model simulations the depolarization of HTC cells is key to the generation of alpha-delta sleep. While the origin of the alpha activity seen during alpha-delta sleep has not been determined experimentally, the importance of the depolarization of HTC cells is in line with the following experimental evidence. Studies show that HTC cells burst at the alpha frequency at depolarized membrane potentials (Hughes et al. 2004). Furthermore, the pharmacological blockade of AMPA and GABA receptors does not prevent HTC cells from bursting at the alpha frequency, suggesting that they are indeed alpha generators (Hughes et al. 2004). In addition, Lőrincz et al. (2009) show that a muscarinic acetylcholine receptor (mAChR) antagonist directly to the thalamus reduces HTC bursting and firing rate in a dose-dependent manner, and that this not only reduces alpha power in the thalamus in a dose-dependent manner but also reduces alpha power in the cortical EEG.

**Awake alpha.** In our model the alpha activity that intrudes into delta activity is unlike spindling but similar to the alpha activity observed over the somatosensory cortex (over the centro-frontal EEG leads) during awake behavior (Haegens et al. 2011; Palva and Palva 2007; Sacchet et al. 2015). Specifically, while spindles wax and wane and last only a few seconds, the alpha activity in our model, like the alpha activity actually observed during alpha-delta sleep, is like awake alpha in that it does not wax and wane and can last for tens of seconds (Roizenblatt et al. 2001).

The manner in which spindles are generated differs markedly from the production of awake alpha. Sleep spindles are generated at hyperpolarized membrane potentials (less than $-65$ mV), while awake alpha occurs when HTC cells are depolarized (greater than $-60$ mV). Furthermore, spindling is a network phenomenon reliant on a ping-pong-like mechanism between RE and TC cells: RE cells inhibit TC cells via GABA, which hyperpolarizes TC cells and engages currents that are more active at hyperpolarized membrane potentials ($I_h$ and standard $I_T$ channels), causing TC cells to spike and in turn excite RE cells via AMPA, starting the cycle anew. While the TC cell population fires at the spindling frequency, it is not true that individual TC cells fire during each cycle of a spindle. In contrast, during awake alpha, a single HTC cell can burst at the
alpha frequency. Since no animal models of alpha-delta sleep exist, we were not able to use the physiological properties of alpha-delta sleep to distinguish it from spindling or from awake alpha.

We note that since spindles do naturally occur during slow-wave sleep, it may be the intrusion of awake alpha-like activity during delta activity that is especially disruptive to the therapeutic effects of normal delta sleep.

The exact frequency range of alpha in the alpha-delta sleep of fibromyalgia patients may be slightly lower than that of traditionally recognized awake alpha; however, this is likely due to the way the awake alpha mechanism manifests during sleep. Specifically, the frequency of alpha activity during alpha-delta sleep may dip to 7 Hz (Hauri and Hawkins 1973; Roizenblatt et al. 2001), which is slightly below the traditional awake alpha band (8–13 Hz), although Sacchet et al. (2015) use 7 Hz as their lower cutoff for awake alpha activity over the somatosensory cortex. Experimental results (Hughes et al. 2004) and our modeling work (Vijayan and Kopell 2012) show that HTC cells, the putative generators of awake alpha, can burst within the awake alpha frequency range or below (e.g., 7 Hz) and the bursting rate depends on their relative level of depolarization—the more hyperpolarized, the slower the frequency. Awakelike alpha activity during sleep may manifest at slightly lower frequencies since thalamic cells tend to be more hyperpolarized during sleep compared with awake states. That is, the depolarization of HTC cells during sleep likely occurs from a more hyperpolarized starting point, resulting in HTC cells firing at a slightly slower oscillation frequency.

Drugs like sodium oxybate that reduce alpha-delta sleep in fibromyalgia patients reduce the pain symptoms of these patients (Moldofsky et al. 2010; Scharf et al. 2003), and the induction of alpha-delta activity via tones played at the alpha frequency or via general slow-wave sleep disruption has been shown to induce fibromyalgia-like symptoms in healthy control subjects (Lenz et al. 1999; Moldofsky et al. 1975). However, the causal relationship between alpha-delta sleep and pain in fibromyalgia patients remains unknown. A putative function of delta sleep is that it serves a homeostatic role by downscaling synaptic strength (Tononi and Cirelli 2006; Vyazovskiy et al. 2009). Therefore one possible causal mechanism linking alpha-delta sleep with the pain experienced by fibromyalgia patients is that the normal downscaling that would occur along the pain pathway does not occur because of the disruption of normal delta activity by alpha activity.

It should be noted that the intrusion of alpha activity during sleep has been observed in some healthy subjects (Scheuler et al. 1983) and occurs predominantly in the frontal EEG channels. The alpha-delta activity observed in fibromyalgia patients occurs at least in central channels (Moldofsky et al. 1975), but the exact spatial extent is not known. A high-density EEG study is needed to distinguish the spatio-temporal patterns of alpha activity that occur during sleep in healthy subjects and in fibromyalgia patients. The anatomical regions, spatial extent, rate of occurrence, and temporal characteristics could all be critical for explaining why alpha-delta activity could have deleterious effects in fibromyalgia patients.


